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Surgery:

The Effect of Immunosuppression on Cancer

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Since 1948 when Farber and his colleagues[17] introduced aminopterin in the treatment of acute leukemia of childhood, the field of cancer chemotherapy has grown spectacularly. Today, a vast selection of drugs are available to treat every variety of cancer. One of the effects of many of these agents is impairment of antibody synthesis and cell mediated immunity. These immunosuppressive effects have been used therapeutically to prevent and control rejection of organ transplants. The immunosuppressive agents have also been used to treat a variety of clinical states including chronic hepatitis, ulcerative colitis, Crohn's disease, glomerulonephritis, sarcoidosis, bronchial asthma, uveitis, rheumatoid arthritis, psoriasis and other chronic skin diseases.

Apart from their cytotoxic side effects the cancer chemotherapeutic agents have direct or indirect mutagenic, teratogenic and oncogenic effects. These have been frequently demonstrated in experimental animals and in lower forms of life.[4, 7, 16, 30, 32, 33, 35, 58, 60, 75] The present report is concerned with their potential oncogenic properties in man. Evidence has been accumulated from three groups of patients: 1) Organ transplant recipients treated with immunosuppressive compounds; 2) Patients with a variety of nonmalignant diseases treated with immunosuppressive agents; 3) Patients with malignancies who received cancer chemotherapy.

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ORGAN TRANSPLANT RECIPIENTS

Since the Fall of 1968 an informal Tumor Registry has been maintained in Denver to record all cases of cancer encountered in organ homograft recipients.[49–52] Tumors were encountered in three groups of patients: Cancers that appeared after transplantation; cancers inadvertently transmitted with the organ homograft; cancers that were present before transplantation. The role played by the immunosuppressive drugs in each of these categories must now be considered.

Cancers That Appeared After Transplantation

In previous reports[49–52, 68] we have indicated that an organ transplant recipient maintained on chronic immunosuppressive therapy has a 5 to 6% chance of developing a malignant tumor. This risk is approximately 100 times greater than in individuals in the general population in the same age range. Through September 15, 1972 we collected details of 122 cases from transplant centers throughout the world (Table 1) and incomplete information on approximately another 25 cases. The 122 patients had 125 types of tumor of which 76 were of epithelial origin (61%) and 49 (39%) were mesenchymal. The most common epithelial lesions were various skin cancers (27 cases—36%), carcinomas of the cervix (11 cases—14%) and carcinomas of the lip (11 cases—14%). The most common mesenchymal tumors were various types of solid lymphoma (42 cases—86%) of which the most prominent group were the reticulum cell sarcomas (30 cases—61%). A most unusual feature of the lymphomas was their predilection for the central nervous system which occurred in 20 of 41 cases (49%). In 17 instances (41%)

TABLE 1
Types of Tumors

Epithelial Tumors		Mesenchymal Tumors	
(76 in 74 patients)		(49 in 48 patients)	
Skin cancers	27*	Reticulum cell sarcoma	30‡
Carcinoma of cervix	11	Kaposi's sarcoma	4‡
Carcinoma of lip	11*	Unclassified lymphoma	3
Carcinoma of lung	4	Hodgkin's disease	1
Carcinoma of colon	2	Lymphosarcoma	1
Hepatoma	2	Plasma cell lymphoma	1
Endometrial carcinoma	1	Lymphoreticular malignancy	1
Carcinoma of bile ducts	2	Lymphoma	1
Dysgerminoma of ovary	1	Leukemia	2
Embryonal cell carcinoma of testis	1	Rhabdomyosarcoma	1
Adenocarcinoma of breast	2	Leiomyosarcoma	2
Carcinoma of floor of mouth	1	Synovial sarcoma	1
Widespread squamous cell carcinoma (primary site unknown)	1	Oligodendroglioma	1
Carcinoma of stomach	1		
Carcinoma of pancreas	1†		
Carcinoma of kidney	2		
Malignant melanoma of retina	1		
Carcinoma of thyroid gland	1		
Carcinoma possibly of suprarenal origin	1		
Miscellaneous undifferentiated carcinoma	3†		

* One patient had a carcinoma of the lip and a carcinoma of the forehead.
† One patient had a well differentiated carcinoma of the pancreas and a markedly anaplastic carcinoma in the mediastinum.
‡ One patient had a reticulum cell sarcoma of the brain and Kaposi's sarcoma of the skin.

the central nervous system was the only area affected. These figures contrast with a 0.04% to 1.5% involvement of the central nervous system in two large series.[55, 57]

The cancers generally occurred in young people (average age 36, range 8 to 70 years) of which 37% were over the age of 40 years. The average time of appearance of the tumors following transplantation was 28 months (range 1 to 92 months). In 16 instances (13%) the neoplasms made their appearance within the first 4 months after transplantation. It is possible that at least some of these tumors or even some of those with a later appearance were already present at the time of transplantation, but were small and undetected, and grew rapidly under the influence of the immunosuppressive therapy.

It is important to consider whether the cancers were inadvertently transplanted from the organ donors. The 122 recipients received their transplants from 137 donors, 62 living volunteers and 75 cadavers. None of the living donors has manifested evidence of cancer during follow-up periods as long as 9¾ years. Two cadaver donors had medulloblastomas, whereas the recipients subsequently developed a gluteal reticulum cell sarcoma and a gastric leiomyosarcoma respectively. The tumors in donor and recipient were morphologically distinct and there was probably no etiologic connection unless they were both caused by an oncogenic virus that was transmitted with the donor kidney. A further cadaver donor had had carcinoma of the colon resected five years previously

but was apparently free of tumor at the time of transplantation. The recipient developed a cerebral reticulum cell sarcoma.

Almost all of the patients received immunosuppression with azathioprine and prednisone. Other immunosuppressive agents used were ALG (38 cases, in 2 cases after the appearance of tumor), Actinomycin (39 cases), roentgen therapy to the homograft (45 cases), splenectomy (41 cases), thymectomy (7 cases), thymic irradiation (2 cases), thoracic duct lymph drainage (7 cases), endolymphatic radiation (1 case), total body irradiation (1 case), cyclophosphamide (3 cases), methotrexate (1 case), 6-mercaptopurine (1 case), and azaserine (1 case).

Treatment of the epithelial lesions of skin, lip and uterine cervix followed conventional lines and was usually successful. However, many patients with cancers of the skin tended to have multiple lesions and in two instances the tumors involved the regional lymph nodes. In two instances not included in the present series because of incomplete data, the skin tumors metastasized and killed the patients. Epithelial tumors other than those mentioned above had a much worse prognosis and either caused or contributed to the patients' deaths. The overall survival in patients with epithelial cancers was 44 of 74 (59%). The outlook for recipients with mesenchymal neoplasms was even more gloomy in that only 11 of 48 patients (23%) are still living. Experience thus far is limited, but it appears that conventional cancer therapy combined with reduction or cessation of immunosuppression may permit the patient's immune system to recover and destroy the neoplasm. Five of the current survivors with highly malignant tumors were treated in this way with apparent eradication of the lesion. One of these patients is still alive more than four years after treatment of a cerebral lymphoma. In addition, two patients with widespread tumors treated in this fashion, who died of infection or homograft failure, were found to be free of cancer at autopsy.

Transplanted Cancers

Table 2 is a summary of cases in which kidneys were removed from donors who had cancer at the time of donation or who manifested evidence of the disease some months afterwards. Five of the 33 transplants were from living donors and 28 from cadavers, of which the great majority had widespread cancer. In each case the transplanted kidney appeared to be grossly free of tumor. However, in some cases macroscopic or microscopic evidence of cancer was found in the contralateral kidney and in several instances this was an indication for removal of the transplant.

TABLE 2
Fate of Patients Who Received Kidneys from Donors with Cancer
(Excluding primary cerebral tumors)

Total number of recipients		33
Recipients with no evidence of cancer		19
Cancer in transplanted kidney only		4
Cancer involved kidney and adjacent structures		2
Cases with distant spread of cancer		8
Died of metastases	4	
Rejection of tumor	3	
Died of other causes	1	

Two of the living donors were apparently free of tumor at the time of nephrectomy but subsequently developed cancer of the rectum and pancreas respectively. It is questionable whether the tumors were present at the time of donation and both recipients are well at 13 and 18 months post-transplantation respectively. In two further instances "free" kidneys removed from patients who were operated on for cancer were used. One was from a patient with carcinoma of the colon compressing the ureter, while the second was the seat of a hypernephroma. This latter kidney was deliberately transplanted into a physician dying of renal failure in whom no other suitable donor was available. Severe rejection of the homograft occurred at 12 weeks in spite of immunosuppression. However, the neoplastic tissue survived and was vigorously invading adjacent structures at the time of the patient's death three weeks later.

The fifth living donor was found to have a nodule in the kidney at operation. The nodule was removed and, as a frozen section examination suggested a benign lesion, the kidney was transplanted. However, a permanent section raised the suspicion of ma-

lignancy, and the kidney was removed at 48 hours. The recipient remains free of tumor 17 months after a second transplant and immunosuppressive therapy.

Of the 33 recipients, 19 showed no evidence of tumor either at autopsy or during follow-ups which have ranged from 1 to 32 months. Presumably the kidneys were either free of cancer, or transplanted malignant cells failed to become established in the host. In four more patients, tumor was found in the kidneys when they were removed within the first 16 days after transplantation. In two more recipients (including the patient with hypernephroma mentioned above) the kidney and adjacent structures were involved by cancer, while in eight more patients there was also evidence of distant spread of the neoplasm. Four of these eight died of the transplanted cancer and in a fifth, metastatic tumor undoubtedly contributed to the patient's death. Immunosuppression was discontinued in the remaining three patients and the cancers apparently underwent rejection.[79, 82] One of these recipients is well 97 months post-transplantation despite further immunosuppressive therapy given for two subsequent renal transplants, each of which functioned for 12 to 18 months. The second patient died several months after cessation of immunosuppression and was found to have no evidence of tumor at autopsy. The third recipient had a suspected cerebral metastasis, but no evidence of this or of residual cancer in the kidney was found at autopsy five months after immunosuppression was discontinued.

Cancers Present Before Transplantation

Fifty three patients had cancers within the five years preceding transplantation (Table 3). The table does not include cases of leukemia or advanced cancers treated with bone marrow or splenic transplantation, nor cases with a follow-up of less than two months. A number of patients who underwent liver replacement for hepatoma are therefore excluded from this study. In 14 of the 53 cases the tumor did not involve the organ undergoing replacement (skin 6; bladder 2; thyroid 1; parathyroid 1; parotid 1; breast 1; cervix of uterus 1; recurrent leiomyosarcoma of small bowel 1). In 39 cases transplantation was performed specifically for treatment of cancer of one or both kidneys (21 cases), primary or metastatic cancer of the liver (17 cases) and carcinoma

TABLE 3
Effect of Immunosuppression on 53 Patients with Pre-Existing Cancers*

Type of Cancer	Number of Cases	No Recurrence	Recurrence or Metastases	Development of Unrelated De Novo Tumors	Tumor Not Removed, Remained Unchanged
Liver cancers	17	7	9	—	1
Renal and urethral cancers	21	12	7†	3†	—
Laryngeal cancer	1	—	1	—	—
A. Total of all cases who had transplantation for cancer	39	19	17†	3†	1
B. Cancers incidental to transplantation	14	9	5	—	—
C. Total of all cases	53	28	2†	3†	1

* Treated 5 years or less before transplantation, excluding cases of leukemia and advanced cancers treated by bone marrow or splenic transplantation; and cases with a follow-up of less than 2 months.

† One patient died of metastases of a urethral carcinoma but also had a de novo skin cancer.

of the larynx (1 case). Three of the kidney patients underwent transplantation for renal failure and an incidental carcinoma of the kidney was found in two and of the ureter in one. Where transplantation was performed in the treatment of cancer, the neoplasm appeared to be localized and resectable so that there was hope of obtaining a "cure."

Nine (64%) of the 14 patients with a variety of neoplasms remained free of tumor for 7 to 60 months after transplantation and 5 (36%) developed recurrent or metastatic cancer in a follow-up of 2 to 36 months.

In the 21 patients who had transplantation for renal or ureteral neoplasia, 7 (33%) had recurrent or metastatic tumor. One of these recipients had a pulmonary metastasis resected at 3 months and is apparently free of tumor 56 months after transplantation. Twelve patients (57%) were free of cancer after follow-ups ranging from 2 to 48 months. Three of the 21 recipients (14%) developed de novo tumors of a completely different type from their original neoplasms, but one of these died of metastases of the ureteral carcinoma.

Of the 17 patients who underwent transplantation for hepatic tumors, 9 (53%) died with recurrent tumor in follow ups ranging from 2½ to 14 months, and 4 (23%) died of other causes 2½ to 4½ months after transplantation and manifested no evidence of cancer at autopsy. One patient (6%) in whom the original tumor was not removed died of infection at 8 months and showed no apparent progression of the neoplasm during this time. Three patients (18%) are alive 30 to 42 months after transplantation and are apparently free of tumor. The individual who underwent laryngeal transplantation died 10 months later of recurrent tumor.

Thus, of the 53 recipients, 28 (53%) have no evidence of tumor in follow-ups ranging from 2 to 42 months. Twenty-two patients (41%) developed recurrent or metastatic cancers, 3 (6%) (one of whom also manifested metastasis of a ureteral carcinoma) developed de novo tumors of a completely different type from their original neoplasms, and in one (2%) the non-resected tumor remained unchanged.

PATIENTS WITH NONMALIGNANT DISEASES TREATED WITH IMMUNOSUPPRESSIVE AGENTS

Thirty patients suffering from chronic cold hemagglutinin disease,[80] rheumatoid arthritis,[19] the nephrotic syndrome,[64] systemic lupus erythematosus,[37, 41] ulcerative colitis[48] or psoriasis[13, 24, 44, 54, 56, 63] were treated with immunosuppressive agents and developed cancer (Table 4). In the case of the first four conditions it might be argued that the

TABLE 4
Development of Cancers in 30 Patients with Nonmalignant Diseases Treated with Immunosuppressive Agents

Disease	No. of Cases Treated	Major Agent Used*	Type of Cancer
Chronic cold hemagglutinin disease	1	Chlorambucil	Reticulum cell sarcoma (1)
Rheumatoid arthritis	4	Cyclophosphamide	Lymphoma (2); leukemia (2)
Nephrotic syndrome	2	Azathioprine	Lymphoma (1); bronchial carcinoma (1)
S.L.E.	2	Azathioprine	Lymphoma (1); malignant melanoma (1)
Ulcerative colitis	1	Azathioprine	Carcinoma of colon (1)
Psoriasis	20	Methotrexate (19); Aminopterin (1)	Various visceral cancers (17); skin cancers (3)

* In some cases more than one agent was used.

immunosuppressive agents played no role in the development of the tumors as these are autoimmune diseases in which an increased incidence of cancer, particularly lymphoma, has been reported.[22, 50] Similarly, the administration of azathioprine to the patient with ulcerative colitis may have been purely fortuitous in a condition which is frequently complicated by carcinoma of the colon. However, these arguments do not apply to psoriasis which is not usually associated with cancer, unless the patient has been treated with a carcinogenic agent such as arsenic. The development of cancer in twenty psoriatic patients chronically treated with methotrexate or with the closely related compound, aminopterin, must therefore be regarded with the gravest suspicion.

PATIENTS WITH MALIGNANCIES WHO RECEIVED CANCER CHEMOTHERAPY

Table 5 is a summary of patients who received prolonged cancer chemotherapy for one type of neoplasm and subsequently developed a new cancer of a different type.[1–3, 5, 9, 11, 12, 15, 20, 25, 26, 29, 31, 34, 36, 38–40, 42, 43, 45–47, 53, 61, 62, 66, 73, 76, 78, 81] Were the anticancer drugs the cause of these tumors or could these have occurred spontaneously? It is well recognized that a patient with one type of cancer is more prone to develop a second neoplasm. Furthermore, certain tumor associations are widely accepted, including polycythemia rubra vera or myelofibrosis (with myeloid metaplasia) with granulocytic leukemia; the relationship between solid lymphoma and lymphocytic leukemia; and the termination of chronic myelogenous leukemia in acute myeloblastic leukemia. A few of the cases in Table 5 may be of this type. However, certain associations are decidedly uncommon and raise the strong suspicion that the cancer chemotherapeutic agents, while controlling the original neoplasm, may have contributed to the development of the second type of tumor. The development of acute leukemia in 21 patients with multiple myeloma who were chronically treated with anticancer drugs, most commonly melphalan, is one striking example. Another is the development of a solid lymphoma in nine cases of chronic *granulocytic* leukemia. McPhedran and Heath[42] have emphasized the rarity of acute leukemia in chronic lymphocytic leukemia and have mentioned the possibility that the acute leukemia represents a second malignancy rather than a true "blast" phase of chronic lymphocytic leukemia. Numerous isolated cases of a second tumor which appeared while the patient was receiving chemotherapy for cancer are shown in Table 5. In many of these reports the authors raised the question whether the second tumor was induced by the very agent which had controlled the first cancer.

DISCUSSION

The cancer chemotherapeutic agents exert their effects usually by interference with DNA or RNA metabolism and may seriously disrupt the normal function of the cells. These cytostatic or frankly cytotoxic effects are seen not only in cancer cells but also in other vulnerable cells of the host. In experimental animals it has been shown that the agents and their immunosuppressive derivatives may also cause chromosome breaks, depression of immune responses, mutagenic, teratogenic and even encogenic effects.[4, 23, 32, 33, 35, 50, 58, 60, 72, 75, 77] It is indeed a paradox that agents which destroy cancer or arrest its growth may themselves be oncogenic.

In man some of these undesirable side effects have been demonstrated. Chromosome breaks,[27, 28, 59] nuclear abnormalities,[30, 74] cytologic dysplasia[8, 18, 23, 34, 43, 45, 65, 77] and teratogenic effects[14, 30, 67, 69] have also been described.

Several questions have to be answered. Do the anti-cancer and immunosuppressive agents cause cancer in man? If so, by what mechanism? What is the effect of these agents on existing cancers?

The answer to the first question is provided mainly by experience gained in organ homograft recipients. In the University of Colorado-Denver Veterans Administration Hospital series we have repeatedly reported a 5 to 6% incidence of de novo cancers in renal homograft recipients treated with chronic immunosuppressive therapy.[49–52, 68] At the present time we have found de novo tumors in 22 of 390 recipients (5.6%) with a potential follow up of from 6 months to almost 10 years. The additional 100 cases

TABLE 5
New Malignancies in 61 Patients with Cancer Treated with Chemotherapy

Initial Cancer	Number of Cases	Major Agent Used*	Number of Cases	Second Cancer	Number of Cases
Multiple myeloma	21	Melphalan;	19	Acute leukemia;	21†
		Cyclophosphamide	2	Basal cell carcinoma of skin	1†
Chronic granulocytic leukemia	13	Busulfan;	10	Reticulum cell sarcoma	4
		Multiple;	2		
		Urethane	1	Lymphosarcoma	3
				Hodgkin's disease	2
				Carcinoma of vulva	1
				Carcinoma of breast	1
				Carcinoma of pancreas	1
				Carcinoma of lung	1
Chronic lymphocytic leukemia	3	Chlorambucil	3	Myelomonocytic leukemia	1
				Acute myeloblastic leukemia	1
				Acute leukemia	1
Polycythemia rubra vera	9	Melphalan;	7	Acute leukemia	6
		Triethylene melamine	1	Glioblastoma multiforme	1
		Busulfan	1	Carcinoma of prostate	1
				Carcinoma of colon	1
Lymphosarcoma	4	Cyclophosphamide	4	Carcinoma of skin	2
				Carcinoma of stomach	1
				Carcinoma of bladder	1
Hodgkin's disease	3	Multiple;	2	Carcinoma of bladder	2
		Cyclophosphamide	1	Carcinoma of lung	1
Choriocarcinoma	3	Methotrexate	3	Carcinoma of cervix in situ	2
				Hodgkin's disease	1
Carcinoma of ovary	3	Thiotepa;	2	Acute leukemia	3
		Methotrexate	1		
Adenocarcinoma of lung	1	Thiotepa	1	Acute leukemia	1
Primary myelofibromatosis	1	Cyclophosphamide	1	Reticulum cell sarcoma	1

* In some cases more than one agent was used.
† One patient developed acute leukemia and a basal cell carcinoma of the skin.

collected from transplant centers throughout the world confirm these findings.

These conclusions are reinforced by experience gained with neoplasms inadvertently transplanted with kidneys obtained from donors with cancer. It is very rarely possible to transplant a malignant tumor from one healthy human to another. The tumor cells are recognized as "foreign" by the host's defenses and are readily destroyed. However, if the normal defense mechanisms are impaired by chronic immunosuppression it is possible for the transferred malignant cells to become established in the transplanted

organ, invade the surrounding tissues and metastasize widely. If the immunosuppressive therapy is discontinued before the cancer has completely sapped the host's resistance, it is possible for the immune defenses to recover and to reject the cancer cells. This method of treatment was successfully employed in several cases reported in this paper. Furthermore, it may also be applicable to the management of the more aggressive de novo tumors which arise in organ homograft recipients and which fail to respond to conventional cancer therapy.

The concept that tumors may arise in individuals under chronic immunosuppressive therapy is further strengthened by reports concerning nontransplant patients treated with these agents. This applies particularly to sufferers from psoriasis who received chronic treatment with methotrexate or aminopterin.

How do the immunosuppressive or cancer chemotherapeutic agents cause malignant tumors? The answer here is speculative, but several possibilities exist. First, the drugs may be directly oncogenic. Second, the compounds may potentiate the effects of various environmental carcinogens such as tobacco, sunlight or radiation. Third, the agents may cripple the surveillance function of the lymphoreticular system.[6, 70] Mutations, some of which are potentially oncogenic, are constantly occurring either spontaneously or in response to various stimuli. The mutant cells are normally eliminated by the lymphoreticular system. However, if its function is impaired by chronic immunosuppressive therapy, malignant mutations may survive and cause overt cancers. Fourth, the immunosuppressive drugs may permit oncogenic viruses to become established and cause malignant tumors.

While there is unequivocal evidence that the anti-cancer and immunosuppressive agents may cause de novo neoplasms, their effects on patients with pre-existing tumors are not so clearly defined. In organ transplant recipients with cancer there is a 41% likelihood of recurrence or metastases of the original tumor and a 6% incidence of an unrelated de novo neoplasm. In the present state of our knowledge it is not possible to determine whether the former figure is merely a reflection of the natural history of the cancers or is contributed to by chronic immunosuppressive therapy. In this connection there is an interesting observation by Thomas[71] who treated several patients with acute lymphatic leukemia with total body irradiation, bone marrow transplantation and immunosuppression. In several of the recipients, leukemia recurred but in two instances the lesion involved the transplanted *donor* cells.

In the case of advanced cancers treated with chemotherapy there are a number of reports suggesting that while the original cancer had been controlled the long-term chemotherapy may have caused new cancers. Many of these cases are summarized in the present paper. No doubt there are numerous additional cases which have not been reported. The subject is a very complex one as we have to take into consideration the increased likelihood of a patient with one cancer developing a second neoplasm; the tendency for one form of cancer to change to another related type; and the influence of other therapeutic agents such as radiotherapy which may be oncogenic. In the present series (Table 5) the three most commonly used compounds were melphalan, cyclophosphamide and busulfan—all alkylating agents. These have radiomimetic actions and are known to be mutagenic and carcinogenic in laboratory animals.[4, 33, 75] The same could be said for several other anti-cancer drugs which are not alkylating agents.

While cancer chemotherapy has had some notable successes, as in the treatment of choriocarcinomas, Burkitt's lymphoma, Wilm's tumor and acute lymphatic leukemia, the overall results have been rather disappointing. These have been blamed on unresponsiveness of the tumor to a particular agent, or on subsequent development of resistance to the compound by the cancer cells, or to the toxic effects of the agents used. Another factor, which has received relatively scant attention, is the prolonged immunosuppressive effect of the agents when administered for prolonged periods. Could this be the explanation for the observation that a better objective response and longer

survival was observed when chemotherapy was given intermittently rather than continuously?[10, 21]

The finding that cancer patients treated with chemotherapy may develop entirely new tumors is more of academic than of practical importance and represents the price the patient has to pay for months or years of relief from the original cancer. However, several important lessons do emerge from this study. First, immunosuppressive agents should not be used in nonmalignant diseases such as psoriasis or rheumatoid arthritis unless all other forms of therapy have failed to provide relief. Second, in organ transplantation, donors with cancer should not be used except in cases with primary tumors of the central nervous system which seldom spread to other organs, and even here there may be an increased risk. Third, when a cancer arises in an immunosuppressed patient it may be useful to withdraw or reduce the immunosuppressive therapy in the hope that the host defenses may recover and destroy the neoplasm. Fourth, the studies emphasize the importance of the immune system in dealing with cancer, and suggest that research on immunotherapy should be vigorously pursued.

SUMMARY

Cancer chemotherapeutic and immunosuppressive agents may be directly or indirectly oncogenic. Organ transplant recipients on chronic immunosuppressive therapy have a 5 to 6% chance of developing a de novo malignant tumor. Neoplastic cells may be inadvertently transplanted from donors with cancer. If transferred to an immunosuppressed host such cells may become established and grow within the transplanted organ, invade the surrounding structures and produce distant metastases. If immunosuppression is discontinued before the cancer completely saps the host's resistance, the immune defenses may recover and destroy the cancer.

De novo malignant tumors may arise when immunosuppression is used in treatment of diseases such as psoriasis, rheumatoid arthritis or the nephrotic syndrome. The risk of this complication should serve as a deterrent to the use of this therapy in these conditions except when all other methods of treatment have failed. Organ transplantation and immunosuppressive therapy in patients with pre-existing cancers have a 41% risk of recurrence or metastasis of the original tumor and a 6% risk of the development of unrelated de novo tumors.

There is much circumstantial evidence suggesting that cancer chemotherapy, while allowing control of one cancer, may permit or induce the growth of a second tumor. This risk may be of little practical importance but it is a matter of great biologic interest in terms of the etiology and potential treatment of cancer. One hope for the ultimate eradication of cancer appears to be in the field of immunotherapy.

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